Phenotypic abnormalities in childhood cancer patients; clues for molecular defects?
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Chapter 9

Discussion
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The general aim of the present study was to use clinical observations in greater depth and more detail to add to the search of genes involved in childhood cancer. We therefore set out to examine a large cohort of pediatric cancer patients for body surface phenotypic abnormalities and internal skeletal developmental abnormalities. We searched for patterns of developmental abnormalities that are associated with childhood cancer, in order to find clues for candidate genes and related genetic pathways that are involved in both abnormal morphogenesis and tumorigenesis.

We realize that both pathway defects and environmental factors may lead to phenotypic abnormalities and tumor predisposition. Some of these aspects are discussed in the Introduction and in Chapter 7. However, as this was not the main focus of the study this will not be elaborated here in more detail.

In this general discussion we will explore some of the major points raised by the different parts of this thesis:

A. Phenotypic abnormalities: need for definitions
B. Phenotypic abnormalities: need for normal values in older children and adults
C. Family resemblance
D. Role of clinical morphology in pediatric oncology
E. Private syndromes
F. Skeletal anomalies
G. Childhood tumors: need for better classification systems
H. Identifying the disease genes

A. Phenotypic abnormalities: need for definitions

Earlier studies all had used different terminologies and classifications. Therefore, we started by proposing a uniform terminology and classification system for all phenotypic abnormalities that can be detected in a morphological examination. Terminology and classification were based on four major sources: 1. Recommendations on terminology of an international working group, 2. An editorial comment on studies of minor anomalies by Opitz, 3. Aase’s text on clinical morphology, and 4. The London Dysmorphology Database (LDDB). We searched the literature for a comprehensive list of definitions of all phenotypic abnormalities, approved by an international group of experts in clinical morphology, but were unable to find one. Therefore we used the definitions provided by the LDDB, Aase’s text on clinical morphology, and the Handbook of normal physical measurements by Hall et al. Although these sources are internationally the most commonly consulted sources for definitions, those definitions are not based on international agreement. Studies in the past often have used different definitions, hindering the comparison of data from different study and control populations. To promote the use of a uniform language in clinical morphological studies, we propose that a list of definitions of all phenotypic abnormalities
be created, and approved on by an international working group of experts in the field of clinical morphology. Definitions of measurable items should be accompanied by clear ‘measurement instructions’ and appropriate normal values, building on the text by Hall et al. 5. Qualitative, non-measurable phenotypic abnormalities should get clear descriptions, accompanied by multiple photographs per phenotypic abnormality, to show their full range of presentation over a life-span. Furthermore, for each phenotypic abnormality, the (suspected) cause and pathogenesis should be described and updated at regular intervals. This will require an enormous effort from all experts in the field. However, the importance cannot be overestimated, and the result will prove a major, essential element in future clinical morphological studies, and create a powerful tool for the translation and interpretation of the recorded findings in individuals and groups with common or rare disorders.

B. Phenotypic abnormalities: need for normal values in older children and adults
Besides clear definitions of phenotypic abnormalities, it is also necessary to determine the incidence of those phenotypic abnormalities in the general population. Normal values are indispensable for:
1. Validation of frequency dependent classifications, i.e. minor anomalies and spectrum variants, in the classification list 6, and 2. Comparison with frequencies of phenotypic abnormalities found in specific patient groups in order to properly evaluate (patterns of) phenotypic abnormalities for ‘disorder-specificity’.

In chapter three, we use the childhood cancer cohort itself as an internal control, to detect specific associations between (patterns of) phenotypic abnormalities and individual tumor groups. This may lead to an underestimation of associations, as it will probably dilute the strength of the tumor predisposition pattern. We expect that with the availability of normal values, patterns will become much clearer, allowing a better estimation of their biological importance.

A careful review of the literature has shown only four studies describing the prevalence of phenotypic abnormalities in newborn infants from the normal population 7-10. All studies concluded that minor anomalies can be utilized as indicators of altered embryonic differentiation since they are significantly more common in individuals with an obvious major defect of embryonic development. The studies were performed in newborn infants, all with a similar sample size (Marden et al.: n=4,412, Mēhes: n=3,176; Merlob et al.: n=3,762; Leppig et al.: n=4,305). Differences in results between the three most detailed reported studies 7,8,10, may be accounted for by differences in study design 10. Different lists of phenotypic abnormalities were used, with different definitions, and different terminology and classification. This again underlines the need for the generation and use of an internationally accepted terminology and classification system.

Remarkably, no studies have ever been performed in control populations consisting of older children or adults. As changes of anomalies occur with growth, and the detection rate may be different at different ages 11,12, prevalence figures for morphological findings in newborn infants may not be correct in other age groups.
We conclude there is a great need for a study in older children, to enable studies on (possible) developmental etiologies of many different pediatric disorders. We have initiated such a study in 2004, with financial support from the Stichting Steun Emma Kinderziekenhuis. The control group will be constituted of 1,000 Caucasian children from elementary schools in the age classes 9 and 10 years old. They will be examined by a physician trained in clinical morphology, during their routine medical and psychosocial screening performed by nurses from the community health care department in the region of Haarlem. All children in the region will undergo this screening, while in the 4th grade of elementary school. This age group allows a maximum level of growth and development on one hand, and the lowest possible selection bias caused by active withdrawal of certain children, or scattering over different school types in the older age groups.

C. Family resemblance
Besides use of unrelated controls, several studies included sibs and parents of cases: three registry and interview-based studies reported an equal incidence of (often) major anomalies in sibs and unrelated controls $^{13-15}$, while two others showed a slightly $^{16}$ or significantly $^{17}$ higher incidence in sibs (see Chapter 1, paragraph 7). In the latter study by Baptiste et al. $^{17}$, the high incidence of anomalies in sibs and parents was attributed to the presence of several families with neurofibromatosis in the cohort, a syndrome known for its specific pattern of phenotypic abnormalities and predisposition for CNS tumors. Méhes was the only investigator to study the presence of minor anomalies, based on the actual clinical morphological examination of children with cancer, their sibs and parents $^{18-20}$. He consistently found a significantly higher incidence of minor anomalies in cases and their sibs, compared to parents and age-matched controls. Méhes rightfully concluded that an increased prevalence of anomalies in sibs of children with acute lymphoblastic leukemia (ALL) "cannot be regarded as a sign of predisposition for leukemia. One can only speculate on a possible recessive association of mild errors of morphogenesis with ALL, on possible maternal inheritance, or on developmental genes that may be involved in the processes of malignancy and disturbed morphogenesis as well" $^{20}$. We agree that sibs with a similar pattern of phenotypic abnormalities should not automatically be regarded as cancer-prone. However, when this pattern of phenotypic abnormalities has proven to be a strong independent factor, indicating significant tumor predisposition - in other words, when this pattern appears to represent a (new) tumor predisposition syndrome - sibs with the same phenotype do have this predisposition syndrome and are cancer-prone indeed. This is illustrated by the study of cases with CNS tumors and their families, in which the higher incidence of anomalies in relatives was caused by the contribution of an already known tumor predisposition syndrome, i.e. neurofibromatosis $^{17}$. However, in many syndromes the 'cancer part' of the phenotype may be of low penetrance. Phenotypes of affected relatives will show considerable overlap in the highly penetrant characteristics, but less so in the low penetrance manifestations $^{21}$. Several disorders illustrate that, even within
the same family, identical mutations may be associated with a phenotype that varies in age-at-onset and severity of symptoms. Examples are a wide variety of disorders, such as hereditary long-QT syndrome, renal-coloboma syndrome, or Charcot-Marie-Tooth disease \(^\text{21}\).

Nevertheless, studying low penetrance predisposing genes is useful. According to Ponder \(^\text{22}\), the largest category of inherited tumor predisposition, in terms of the contribution to cancer incidence, is the one with the weakest genetic effects: tumor predisposition without evident family clustering, via low penetrance tumor predisposition genes (see Chapter 1, paragraph 3). The study of weak cancer predisposition is of interest both for public health implications \(^\text{23}\), and because it may point to a wider range of processes that are relevant to cancer development, and to interactions between these \(^\text{22}\). It may give clues for modifier genes, either affecting the probability that tumorigenic alterations will occur, or influencing the effects a tumorigenic pathway event will have on the cellular phenotype (see Chapter 1, paragraph 2).

From population studies on the risks to develop breast cancer, we know that the risk for breast cancer for close relatives of a case is increased two-fold, and is about the same for the mother, sisters or daughters of a proposita \(^\text{22}\). However, this equal penetrance in close relatives seems not to hold for minor anomalies: in Méhes' studies, sibs had a higher incidence of minor anomalies, approximating that of cancer cases, but their parents did not \(^\text{18-20}\).

Clear indications for taking a detailed family history and clinical morphological examination in relatives are difficult to provide, as these are strongly individually determined. It should at least be performed in case a syndrome diagnosis in the proposita is made or suspected, as such a diagnosis may have consequences for the family, both regarding tumor surveillance, occurrence of other physical, cognitive, and behavioral symptoms, as regarding pattern of inheritance and in case prenatal counseling is relevant. Furthermore, the study of relatives may show complementary characteristics, broadening the phenotype, and possibly leading to the recognition of the syndrome in the proposita. The family described in Chapter 6 may serve as an example in this way: the same genetic defect led to minimal phenotypic abnormalities in a mother, and a lethal phenotype in one of her children, illustrating that the phenotype variability of a syndrome can be vast, even within families.

Examination of relatives of a proposita may also lead to detection of similarly affected persons and recognition in a patient with a 'private' syndrome of a hitherto undescribed 'new' entity.

D. Role of clinical morphology in pediatric oncology

In Chapter 2 we describe the value of standard clinical morphological evaluation of childhood cancer patients. We diagnosed a known syndromic entity in 45 patients (4.2%) and we suspected a syndrome in another 35 patients (3.3%). The percentage of 7.5% of patients with a proven or suspected syndrome is considerably higher compared to the prevalence of syndromes in the general population. This underlines that early (epi)genetic defects or environmental factors are of major importance for childhood tumorigenesis.
Twenty-three of the 45 detected known syndromes were detected only during this study, indicating that standard pediatric care can be insufficient to detect clinically important syndrome diagnoses in children with cancer. We propose that all children diagnosed with a malignancy be screened by a clinical geneticist or a pediatrician skilled in clinical morphology for clues pointing to an underlying developmental pathogenesis and cause, serving four goals: 1. To improve the care and cure of childhood cancer patients, as the detection of certain tumor predisposition syndromes will enter a standardized screening program, in order to recognize earlier subsequent malignancies, possibly improving their prognosis. Some tumors may have a different prognosis, requiring different therapy when concurring with a specific syndrome, as has been shown for gliomas in patients with neurofibromatosis. 2. Better knowledge of an underlying syndrome diagnosis is important for the patient and his/her family, as it leads to better understanding and acceptance of their medical history, and can gain an insight into an expected prognosis, 3. Relatives at risk for the same syndrome diagnosis, and the possibly associated tumor risk can be traced, 4. Better knowledge of the incidence of syndromes in children with cancer may lead to the recognition of constitutional defects or environmental factors, previously unknown to be involved in pediatric oncogenesis. Studies in children with cancer for morphological traits should not only be performed on a local basis. International screening of all childhood cancer patients will finally give clear insight in the true syndrome-tumor concurrence, necessitating precise description of syndromes and concurring tumors. This way syndromes may acquire a valid 'tumor predisposition certificate', or loose this certificate. At the same time concurrence of tumors may provide information on syndromes with unresolved cause. In the early years of clinical morphology much effort was put in the exact delineation of syndromes. In the last 10 to 15 years geneticists have put to greater emphasis on the study of the natural history of syndromes, paying attention to all diverse aspects. As stated above, the study of tumor concurrence and predisposition should be one of the important aspects studied.

E. Private syndromes
Some may question the value of so called 'private syndromes'. It should be realized that all now well-known and established syndromes once started as case reports, and were presented as new 'syndrome like patterns' or 'private syndromes'. Only the sharing of those valuable cases led to the recognition and delineation of those syndromes as established entities. It helped clinicians and biologists in the past to discern homogeneous patient groups, leading to better patient care, and enabling the search for their underlying defects. Delineation of patterns in morphological characteristics of 'private syndromes' in children with cancer can be expected to work in a similar way.

F. Skeletal anomalies
Gorlin syndrome serves as an example for constitutional mutations that lead to skeletal anomalies and other phenotypic abnormalities. The same mutation may result in abnormal cellular proliferation
Chapte rr 9
predisposin gg  th e  affecte d  individua l fo r  cancer . W e  studie d  thi s  i n  ou r  stud y  o n  ri b  anomalie s  i n  childre nn  wit hh  acut e  lymphoblasti c  leukemia , astrocytom a  an d  ger m  cel l tumors . As  patternin g  o f th e  axia l  skeleto nn  i n  vertebrate s  i s  mainl y  determine d  b y  /-/ox-gene s 28, an d  Hox  gene  expressio n  i s  als o  know nn  t o  pla y  a  rol e  i n  norma l an d  malignan t hematopoieti c  processes , Hox  genes  ar e  likel y  candidate ss  t o  b e  involve d  i n  bot h  th e  formatio n  o f cervica l rib s  an d  leukemia . Disturbance s  i n  Hox  gene  expressio n  ca n indee d  lea d  t o  th e  formatio n  o f cervica l rib s 29. Within  th e  hematopoieti c system , Hox  genes  ar e  expresse d  in  stem cells  an d  immature  progenito r  cells , but  ar e  dow n  regulate d  inn  differentiate d  myeloi d  cell s 30.31. Th e  MLL-gene, a structural  an d  functional homologue  o f Trithorax, a Drosophiia  homeoti c  regulator , controls  th e  maintenanc e  o f expressio n  o f Hox  genes  durin gg  embryogenesi s 32. MLL-gene  translocation s  ar e  involve d  i n  mos t o f infantil e  leukemi a 33. Mice  wit hh  mutations  o f Pc-G  an d  Trithorax-group  (Trx-G)  genes , involved  in  th e  maintenanc e  o f the  expression  o f Hox  genes,  show  bot h  vertebral  anomalie s  (including  cervical ribs)  an d  leukemia  or  lymphoma 34.36. Although  at present  there  are  no  models  describing  th e  relationship  between  Hox  genes  an d  astrocytom a  or  ger m  cel l tumors , relationships  with  neuroblastoma-,  primitive  neuroectodermal tumor-,  an d  medulloblastoma  cell  lines  exist 37.

The  constant  number  o f seven  cervical  vertebrae  i n  all mammals  (except  for sloths  an d  manatees)  suggests  a  strong  selection  against  cervical  ribs  due  to  deleterious  pleiotropic  effects 38. Based  on  th e  study  by Schumacher et al. 39, Galis calculated  that children  wit hh  a cervical  rib  have  a  120-fold  chance  o f early  childhood  cancer  (11.9% vs. 0.1%),  suggesting  childhood  cancer  to  represent  an important  factor  in  th e  natural  selection  against  th e  development  o f cervical  ribs 38. However,  as  discussed  in  chapter 5,  several  critical  remarks  can  be  made  about  th e  study  by Schumacher et al. 39.

In  ou r  study ,  wit hh  an  equal  number  o f cases ,  a  larger  number  o f pediatric  controls ,  multiple  observers  an d  a reconciliation  process ,  th e  base  line  risk  fo r  childhood  cancer  in  children  wit hh  a cervical  rib  is  significantly  increased ,  but  th e  absolute  risk  is  stil l  very  low.  Wit h  an  incidence  o f childhood  cancer  o f 0.2%,  an d  a  birth  rate  o f 200,000  i n  th e  Netherlands  (wit h  very  low  numbers  of death  during  childhood),  8.6%  o f 400 (=34)  childhood  cancer  patients  will  show  cervical  ribs,  compared  to 6.1%  o f 199,600 (=12,175)  controls.  Thi s  means  th at 34  out  o f 12,209  children  wit hh  cervical  rib  anomalie s  will  develop  childhood  cancer,  increasin g  th eir  baselin e  risk  fro m  0.2%  t o 0.3%. Therefore  childhood  cancer  seems  to  present  only  a  minor  selection  against  th e  development  o f cervical  ribs.  Other  factors  seem  o f  more  importance  in  th is  evolutionary  constraint  against  variatio nn  i n  th e  number  o f cervical  vertebrae.  Adults  wit hh  a rudimentary  first  rib  (an  anterior  homeoti c  transformation  towards  eight  cervical  vertebrae)  often  have  thoracic  outlet  syndrome,  impairin g  manual  labor  an d  therefore  und er  natural  circumstances  implying  a  selective  disadvantage 38. However,  of  more  importance  in  present  Western  human  environment  could  be  th e  increased  chance  o f stillbirths. In  more  th an  30%  o f stillborn  fetuses  ossification  centers  were  found  i n  th e  seventh  cervical  prevertebrae. 40-42. These  ossification  centers  appear  in  th e  same  position  as  th ose  of
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thoracic prevertebrae’s future ribs. The high prevalence of ossification centers in the seventh prevertebrae of stillborn fetuses, might be a pleiotropic manifestation of early aberrant HOX-gene expression, other more serious manifestations of this aberrant HOX-gene expression leading to the premature death of these fetuses, imposing a negative selection on the variation of the number of cervical ribs.

Next to chest radiographs, a radiogram of the left hand and wrist is made routinely in many children with cancer, to determine their skeletal age prior to therapy. Skeletal anomalies of the hand and wrist can give valuable clues for the presence of a syndrome, such as Fanconi pancytopenia. Two studies have been performed, reviewing hand radiographs of 69 and 34 patients with ALL, respectively. Both found a higher incidence of skeletal anomalies in ALL cases compared to controls. No studies in larger groups of patients with other forms of cancer are known to us. In 2005, the departments of pediatric oncology, radiology, and pediatric clinical genetics plan to review all hand radiographs performed in the same childhood cancer cohort used for the study on rib anomalies. The study protocol will be followed simultaneously in a large control group consisting of hand radiograms of healthy children which have become available to us. Information on skeletal anomalies found in the cohort will be combined with clinical morphological findings of patients when available. It is hoped that this study will further serve our goal of identifying possible pathways involved.

G. Childhood tumors: need for better classification systems

In studying phenotypic abnormalities in children with cancer the need for a uniform terminology and classification system applies not only for phenotypic abnormalities but also for childhood tumors. Although many international cooperative groups on the individual tumor types have published their classification systems, significant differences still exist. A uniform system will facilitate the international sharing of data for clinical and biological studies. Starting with the main tumor groups, the system should have a branched structure, and for every case classification should be as precise as possible; it should include all clinical, pathological and biological characteristics.

In Chapter 4, we describe (patterns of) phenotypic abnormalities specific for certain tumor types. Studying patterns of anomalies within tumor groups will elucidate intra-syndrome variations of patterns of phenotypic abnormalities; it will distill the key phenotypic abnormalities of a tumor predisposition pattern, specific for that tumor type. However, many known syndromes show a predisposition to various, ‘different’ tumor types. Our search for patterns of phenotypic abnormalities specific for single tumor types will probably prove to be too narrow and rigid. For the so called embryonal tumors of childhood it might be of importance to develop a classification system based on the developmental stage of the embryonal progenitor cells in which the tumor has arisen. Besides the currently used detailed histopathological tumor classification systems such a developmental classification might provide useful grouping of different childhood tumors and
thereby reveal previously unrecognized patterns of phenotypic abnormalities. Tumor biologists, developmental biologists, pathologists, geneticists, and oncologists are encouraged to join in establishing a developmental classification of childhood tumors. Grouping of tumors on a developmental basis may help to discern, evaluate, and comprehend patterns of tumors described in certain patient groups.

H. Identifying the disease genes
Four main strategies for identifying candidate human disease genes are usually distinguished:
1. Linkage analysis: Linkage analysis can be performed especially in large kindreds, in which multiple relatives are affected. 2. Cytogenetic abnormalities: Cytogenetic abnormalities found in a single affected individual have often been the clue for recognition of the causative gene of a syndrome. 3. Phenotype resemblance: Resemblance of a phenotype with established syndromes of which the responsible pathway defects are already known, may give clues for (related) genes involved. Furthermore, resemblance with symptoms in naturally occurring or artificial knockout mice may point to pathways involved in human disease as well. 4. Functional cloning: In functional cloning, information about the cellular function of a gene product is already known. This information can be used to identify the unknown disease gene.

The third strategy of phenotype resemblance best fits to analyze data from the present study. First, new associations between tumors and syndromes will be investigated. This will allow evaluation of known genetic factors responsible for the syndrome, of their possible role in tumorigenesis, an example being the PTPN11 study in neuroblastoma (see Chapter 8). Second, tumor specific patterns of phenotypic abnormalities may show overlap with the phenotype of already known syndromes, and may point at defects in the same developmental pathway. This is illustrated by the SHH-Patched-Gli pathway, in which two entities - Rubinstein-Taybi syndrome and Saethre-Chotzen syndrome, caused by mutations of genes within this pathway (CBP and TWIST, respectively) - show an expressed phenotypic resemblance. Genes of candidate pathways will first be tested in the germline of cases expressing the phenotype. In case a germline mutation is found, the gene will be tested in sporadic tumors. Third, strong patterns of phenotypic abnormalities, not closely resembling a known syndromic entity, may be discussed in a team of (developmental) biologists, embryologists, clinical morphologists and pediatric oncologists working together in so-called ‘developmental workshops’. Fourth, bioinformatic approaches may be helpful to translate tumor(group) specific patterns of phenotypic abnormalities into candidate genes. Large amounts of data on phenotypes of diverse species and a countless number of their mutant-phenotypes are available in public databases. However, the amount of data available is immense, and terminology too divergent to be efficiently searched in databases such as PubMed. This will hinder the integration of already available knowledge. At this moment no tools are readily available that allow adequate and efficient searching through different databases containing data on phenotypes and their
molecular backgrounds. Possibly the use of ontologies may be helpful here. An ontology is a formal way of representing available knowledge in which concepts are described by both their meaning and their relationship to each other \(^{45}\). Unique identifiers that are associated with each concept in biological ontologies can be used for linking and querying other biological and molecular databases. However, phenotype information is quite complex, as can be deduced from its definition: 'phenotype' is the compilation of observable and measurable characteristics of an organism, which result from the interaction of the organism's genotype and the environment \(^{45}\). Phenotype information is currently described as free-text in most biological databases. However, free-text phenotypic descriptions are often database specific, and cannot be queried and compared easily, especially if they lie outside the immediate research focus of the scientist \(^{45}\). The Jackson Laboratory has developed an ontology to code phenotypes of mutant mice (Mouse Phenotype Ontology). The development of a Human Phenotype Ontology to describe clinical morphological entities will allow linking and querying of human, mouse and molecular databases, such as the mouse Gene Expression Database (GXD), the Edinburgh Mouse Atlas Project (EMAP; a graphical database of mouse gene expression in different developmental stages), Ontoexpress (containing tools for exploring microarray data), PubMed (database of the biomedical literature), OMIM (a catalog of human genes and genetic disorders), and AmiGO (a web application for browsing and searching gene ontology and gene associations).

Adding a human clinical morphology ontology and also a childhood tumor ontology to the already existing ontologies will facilitate the integration of knowledge generated by various investigators, originating from different fields of research, each with their own expertise \(^{45}\). This may lead to the recognition of new knowledge, already present in current literature. It will of course require the continuous input from researchers in the different specialties. Moreover the input of specialists in the field of bioinformatics will be indispensable. The combined efforts may finally result in the recognition of genes and pathways involved in morphogenesis, phenogenesis and oncogenesis, and may give us tools for diagnostic, prognostic and therapeutic strategies in syndromes and diseases.
Implications for clinical practice:
- All childhood cancer patients deserve a clinical morphological examination, as this will improve care and cure of children with cancer and their families. Furthermore it will increase our knowledge of the concurrence of syndromes and childhood cancer, which may lead to the recognition of constitutional defects or environmental factors, previously unknown to be involved in pediatric oncogenesis.
- Detailed analysis of family history and clinical morphological examination in relatives of children with cancer should at least be performed in case a syndrome diagnosis in the proband is made or suspected.

Implications for future research:
- A comprehensive list of definitions of all phenotypic abnormalities should be generated, and approved by an international group of experts in clinical morphology
- Normal values of phenotypic abnormalities in older children and adults should be generated
- We encourage large-scale studies on the prevalence of phenotypic abnormalities, in normal children, in patients who had cancer as a child, and their first-degree relatives in order to gain better insight in the value of family resemblance in general, and the value of specific familial patterns of phenotypic abnormalities.
- Although there is a general tendency to undervalue case reports, we encourage the reporting of specific syndrome – tumor concurrences, as this may lead to better syndrome delineation, and generation of new hypotheses on cause and pathogenesis of both syndromes and their concurring childhood tumors.
- Available hand radiographs in our cohort of childhood cancer patients and in a control group should be reviewed for the presence of skeletal anomalies, as this may generate additional clues for factors involved in tumorigenesis.
- A uniform terminology and classification system for childhood tumors should be generated. Furthermore grouping of tumors on a developmental basis may help to discern, evaluate, and comprehend patterns of tumors described in certain patient groups.
- We encourage the development of a human clinical morphology-ontology and a childhood cancer-ontology. It will allow linking and querying of human, mouse, and molecular databases, facilitating the translation of associations of clinical morphological phenotypes and childhood tumors into candidate genes or causative environmental factors. Close cooperation with specialists in the field of bioinformatics is essential in this process.
Electronic-Database Information

URL for data presented herein is as follows:

Mouse Phenotype Ontology, http://www.informatics.jax.org
Gene Expression Database (GXD), http://www.informatics.jax.org
Edinburgh Mouse Atlas Project (EMAP), http://genex.hgu.mrc.ac.uk
OntoExpress, http://vortex.cs.wayne.edu/projects.htm
AmiGO, http://www.godatabase.org/cgi-bin/go.cgi

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